Combinational Drug Therapy Based Mucoadhesive Tablet for the Treatment of Gastrointestinal Tuberculosis

A Synopsis

on proposed plan of

Research work of

Doctor of Philosophy
in
Pharmaceutical Sciences

Submitted by

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CERTIFICATE

This is certified that the synopsis of Vishal Sharma (Registration No. 24DPH002), Ph.D. Research Scholar (Pharmaceutical Sciences) of the School of Pharmacy and Emerging Sciences (SPES) has been finalized and approved in consultation with Research Guiding Committee. The research scholar has successfully delivered his synopsis entiltled, "Combinational drug therapy based mucoadhesive tablet for the treatment of gastrointestinal tuberculosis," on 28.08.2025 in accordance with the academic regulation. The suggestions given by the members have been duly incorporated.

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List of Abbreviations

Sr. No	Abbreviations	Full Form
1	INH	Isoniazid
2	TB	Tuberculosis
3	*M. tuberculosis*	Mycobacterium tuberculosis
4	LTBI	Latent Tuberculosis infection
5	EPTB	Extra pulmonary Tuberculosis
6	BBB	Blood Brain Barrier
7	GIT	Gastrointestinal Tract
8	GITB	Gastrointestinal Tuberculosis
9	KatG	Catalase-peroxidase gene

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1. Introduction

1.1 Tuberculosis

In 1882, Robert Koch identified the tubercle bacillus also known as *Mycobacterium tuberculosis* as the etiologic agent of tuberculosis (TB) [1]. Since his discovery the TB epidemic seems to be unabated spreading in every corner of the globe. TB is a highly contagious air born disease and one of the top causes of death worldwide [2]. Although the disease typically affects the lungs (referred to as pulmonary TB) it can also spread to other parts of the body known as extra pulmonary TB [3]. *M. tuberculosis* can stay dormant for years and persist in the body without any indication of illness in which many people become symptomatic carriers (inactive TB) [4].

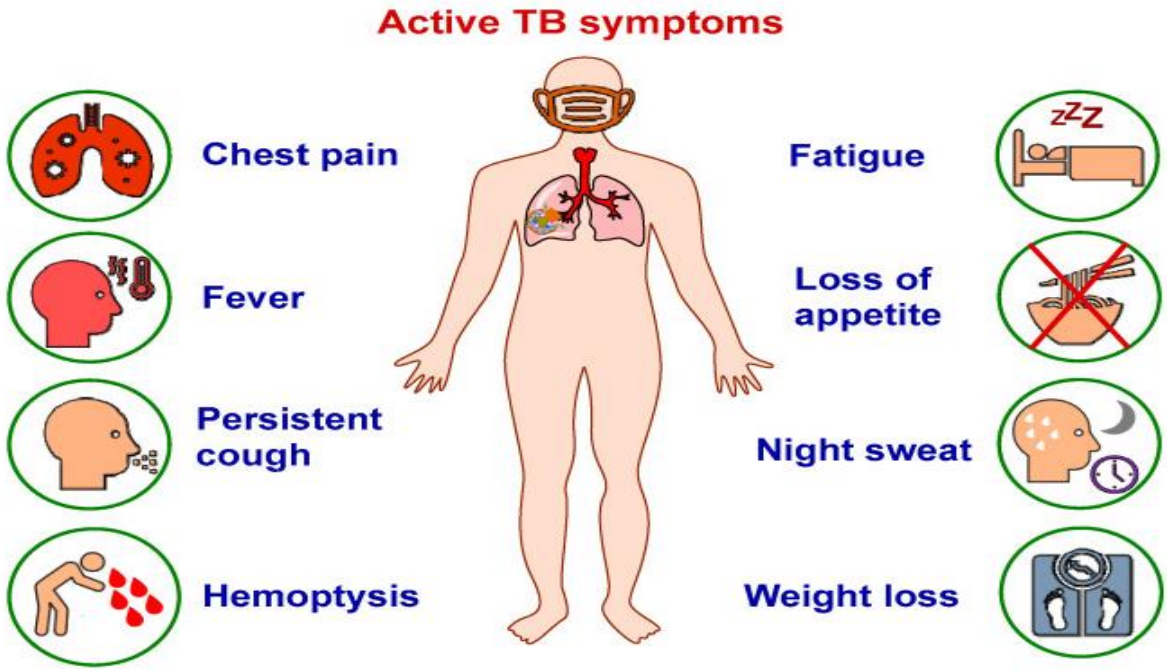


Figure 1:- Symptoms of active TB [5].

According to the World Health Organization (WHO) report of 2022 around one quarter of the world's population (2billion) are latently infected with *M.tuberculosis* In the individuals carrying latent TB infections (LTBI) the estimated lifetime risk for TB reactivation is 5–10%. Indeed, the dormant mycobacteria can be awakened (active TB) particularly in the immune compromised patients such as those who are co-infected with the human immunodeficiency virus HIV. The common symptoms of TB are mentioned in figure 1. Among people living with HIV

approximately 38 million the risk of developing TB is estimated to be 18 times higher than people without HIV [4]. When the stalemate is broken TB reactivation occurs and the bacterial burden soars wherefore the disease becomes symptomic.

1.2 Types of Tuberculosis [6]

Tuberculosis is categorized primarily as Pulmonary TB (affecting the lungs) or extra pulmonary TB (affecting other body parts like lymph nodes, brain, bones, or skin).It can also be classified. As Active TB (contagious and symptomatic) or Latent TB (non-contagious with no symptoms). A severe widespread form called Miliary TB occurs when the bacteria enter the bloodstream and spread throughout the body.

Based on location

• Pulmonary TB	This type primarily affects the lungs and individuals with it may have a cough and an abnormal chest X-ray.
• Extra pulmonary TB	It occurs in organs or tissues outside the lungs.
• Lymph node TB	It is often called scrofula it's the most common form of EPTB.
• Tuberculous meningitis	It occurs in the tissues surrounding the brain or spinal cord.
• Bone and joint TB	It affects skeletal structures.
• Pleural TB	It involves the lining of the lungs.
• Gastrointestinal TB	It affects the digestive system.
• Miliary TB	A serious and rare form where bacteria disseminate to multiple sites in the body through the bloodstream

Based on disease state

• Active TB	Causes symptoms is contagious and requires treatment.
• Latent TB Infection	The bacteria are present in the body but are inactive not causing symptoms and not spread to others. However the bacteria can become reawakened and lead to active TB especially if the immune system is weakened.

Other Classifications

• Drug-Resistant TB:	Caused by Mycobacterium tuberculosis bacteria resistant to standard TB drugs making it harder to treat.
• HIV associated TB:	The HIV pandemic complicates the EPTB scenario with EPTB constituting a significant portion of cases in people living with HIV.

1.3 Pathogenesis of gastrointestinal tuberculosis

Gastrointestinal tuberculosis (GITB) infection follows the same pattern described previously for abdominal TB which includes haematogenous lymphatic direct and ingestion route of spread [7]. In addition, ingestion of milk or food infected with bovine mycobacterium was previously a well- recognized route however the pasteurization of milk and prevention of bovine mycobacterial infection in live stock has made this rare [8]. Whether GITB occurs as a primary infection or as a secondary spread from pulmonary focus is not well-defined co existing pulmonary TB and GITB is reported in 13-67% of the cases with some arguing that this probably is an underestimate due to unrecognized or a symptomatic primary focus [9].

Once the mycobacterium invades into the submucosa through the mucosa of the intestine it initiates a granulomatous inflammatory response including vasculitis with thickening of the submucosa and serosa this leads to ulceration that can perforate or heal by fibrosisn as shown in figure 2. Pathological intestinal TB can manifest as ulcerative hypertrophic ulcero hypertrophic or in fibrotic forms. Complications occur as a result of these different forms of enters it is and present as structures causing obstruction or perforations including fistulas [10].

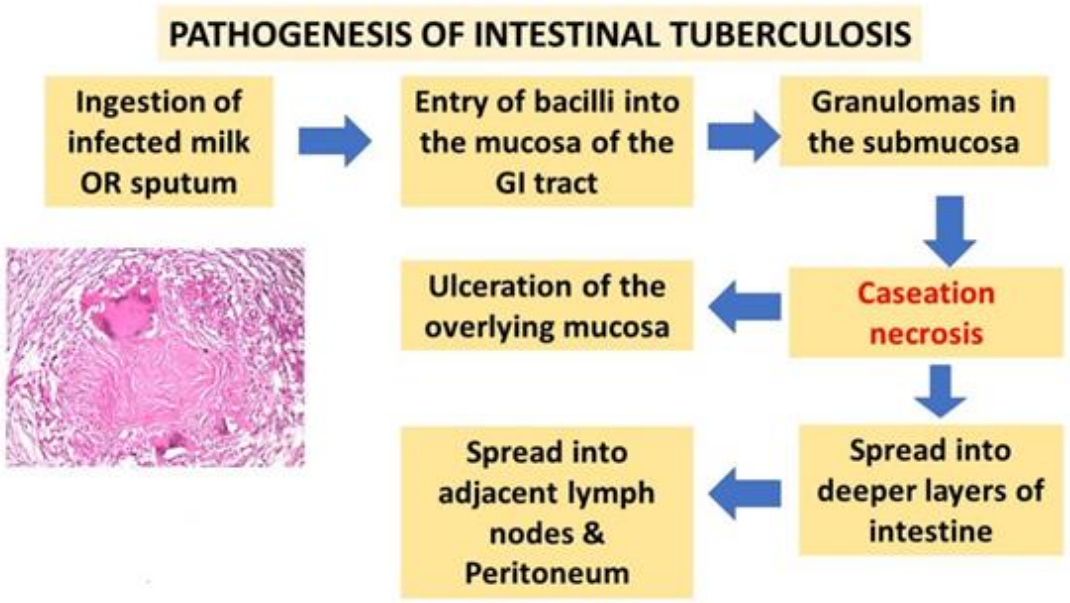

PATHOGENESIS OF INTESTINAL TUBERCULOSIS
Ingestion of infected milk OR sputum
Entry of bacilli into the mucosa of the GI tract
Granulomas in the submucosa
Caseation necrosis
Ulceration of the overlying mucosa
Spread into deeper layers of intestine
Spread into adjacent lymph nodes & Peritoneum

Figure 2: **Clinical Presentation of Gastrointestinal Tuberculosis [11]**

1.4 Early diagnosis and Clinical presentation of gastrointestinal tuberculosis

TB can involve any site of the GIT from the esophagus to the anus, including the perianal region. However, it has a predilection for the ileocecal region which is the most commonly infected site accounting for 44-84% of all GITB cases. The physiology and anatomic pathology of a constricted ileocecal region which leads to long contact time increased absorption and abundant lymphatic tissue explains the predisposition. The other common sites of involvement include caecum, ileum and ascending colon, transverse colon, descending colon, jejunum and rectum. It rarely infects the upper GIT (esophagus, stomach, duo denum) and anus.

2. Literature Review

- **Li *et al.*, 2025,** demonstrated that in a 2025 animal model study the administration of first line anti tuberculosis drugs (including ethambutol) causes significant modulation of the gut microbiota they further show that Bacteroides fragilis 839 ameliorates liver injury induced by anti-TB therapy via anti-inflammatory effects and microbiota regulation. These findings suggest that ethambutol as part of the standard regimen, may contribute to gut dysbiosis and toxicity underlining the importance of microbiome-based adjunctive strategies in GITB management [12].

- **Gonchar *et al.*, 2025,** emphasized that intestinal tuberculosis remains a clinical challenge due to its nonspecific presentation and diagnostic overlap with conditions such as Crohn's disease or gastrointestinal malignancy. In their 2025 retrospective review of eight suspected cases histopathology confirmed tuberculosis in five patients, while PCR was positive in four direct microscopy detected acid-fast bacilli in only one case. The authors note that standard anti tuberculosis therapy for GITB commonly includes isoniazid, rifampicin, pyrazinamide and ethambutol for approximately eight weeks followed by isoniazid and rifampicin for four months. They also highlight poor drug penetration into intestinal lesions leading to treatment durations that often extend to 12 months to achieve better outcomes [13].

- **Nieto *et al.*, 2024,** used alamar blue colorimetric assay to assess antimicrobial activity and the effect of drugs on *M.tuberculosis* growth through growth curves. Bacterial load was determined with an in vitro infection model using colony-forming units/ml and cytotoxicity on human monocyte derived macrophages was assessed by flow cytometry. Both paroxetine and nebivolol demonstrated a significant reduction in viable bacteria compared to the untreated group in the in vitro infection model. Collectively their findings demonstrate that the use of paroxetine and nebivolol is a promising strategy to help in the control of tuberculosis infection [14].

- **Wu *et al.*, 2023,** investigated the effects of second line anti tuberculosis medications on intestinal microbiota composition and function in patients with rifampicin resistant tuberculosis. In this cross-sectional study stool samples and clinical data were collected from patients admitted to the Drug-resistant Specialty Department at Hunan Chest Hospital. Metagenomic sequencing and bioinformatics analyses revealed that second-line anti-tuberculosis therapy altered the structural composition of the intestinal microbiota. The relative abundance of *Prevotella copri* decreased while species such as Salmonella enterica Escherichia coli and eleven other conditionally pathogenic species increased significantly during the intensive phase of treatment. Functional analysis showed inhibition of certain biosynthesis pathways including phenylalanine tyrosine and tryptophan while phenylalanine metabolism was significantly enhanced. These findings indicate that second-line anti-tuberculosis medications substantially affect the composition and metabolic function of intestinal microbiota in patients with rifampicin resistant tuberculosis [15].

- **Jena *et al.*, 2023,** conducted a systematic review and meta-analysis of 33 studies including 1969 patients to assess the prevalence, clinical response, and need for interventions in stricturing gastrointestinal tuberculosis. The study found that strictures occurred in approximately 27% of GITB cases with a pooled clinical response to anti-tubercular therapy of around 77% and radiologic or endoscopic resolution of strictures achieved in about 66% of patients. Importantly about 21% of patients required surgical intervention while 14% needed endoscopic dilatation. These findings indicate that strictures are common in GITB and are not always fully reversible with pharmacological therapy highlighting the need for better predictors to identify patients who will respond to anti tubercular therapy versus those who may require invasive management [16].

- **Yu *et al.*, 2023,** role of the gut microbiota in tuberculosis pathogenesis, including intestinal TB. They reported that both pulmonary TB and intestinal TB patients exhibit reduced gut microbial diversity characterized by decreased Firmicutes and increased potentially pathogenic taxa with associated metabolic disruptions such as altered short-chain fatty acid production that may impair mucosal immunity. The authors propose a

gut–lung axis in which gut dysbiosis both contributes to and is influenced by *Mycobacterium tuberculosis* infection suggesting that interventions such as probiotics or postbiotics could serve as adjunctive therapies in TB. This perspective introduces a novel avenue in GITB research, highlighting the potential for targeting the gut microbiome to enhance host defense and improve treatment outcomes [17].

- **Sheikhpour *et al.*, 2022,** designed a study where an isoniazid and fluoxetine-conjugated multi-walled carbon nano tube nano fluid to increase drug delivery efficiency alongside eliminating drug resistance *in vitro*. The prepared nano fluid was tested against *M. tuberculosis*. Expression levels of isoniazid and KatG mRNAs were detected by Realtime PCR. ELISA was applied to measure level so cytokine secretion from infected macrophages treated with the nano delivery system. The results showed that these nano- drug delivery systems are effective for fluoxetine at far lower doses than for free drugs. Fluoxetine also has an additive effect on the effect of isoniazid and their concomitant use in the delivery system can have significant effects in treating infection of all clinical strains of *M. tuberculosis* [18].

- **Valiulin *et al.*, 2022,** investigated the specific activity of the aerosol form of isoniazid in the mouse model of tuberculosis infection the *M. tuberculosis* H37Rv strain. Aerosol delivery was performed using a laminar-flow horizontal nucleation chamber. The inhalation dose was measured in real-time mode using a diffusion aerosol spectrometer. Studies of the specific activity of aerosolized isoniazid reveal that treatment with the aerosol lead to the complete recovery of the experimental tuberculosis infection as early as after 28 days after the start of inhalation treatment while in the animals from the group receiving isoniazid per-orally sole revivable tuberculosis mycobacteria were detected [19].

- **Nesterenko *et al.*, 2021**, developed mucoadhesive tablet using macozin one hydrochloride with a dosage of 500 mg. The influence of the composition of the media and the added excipients on the solubility of macozin one in various bio relevant media the degree of swelling in the liquid and the degree of mucoadhesion of the experimental tablets to the mucus of the pig stomach were evaluated. The HPLC

method was used to evaluate the kinetics of the release of the active substance. In this work, the expediency of creating macozin one-containing gastro-retentive dosage forms with a slow release of the active substance the delay mechanism of which is provided by swelling and increased adhesion to the gastric mucosa has been substantiated [20].

- **Kawish *et al., 2020,*** created Amphoteric in B-loaded isoniazid-conjugated iron oxide nanoparticles by a combination of physical and chemical processes. Strong anti amoebic effects against the harmful amoeba A. Castellanii was intended for these nanoparticles. These nanoparticles demonstrated strong amoebicidal and cysticidal effects according to the findings of antiamoebic investigations conducted against A. castellanii. The authors concluded that the nanoparticles demonstrated strong amoebicidal and cysticidal activities against A. castellanii [21].

- **Zargarnezhad *et al.,* 2020,** developed magnetic nanoparticles in conjugation with Isoniazid to enhance efficacy against both mycobacterial and non-mycobacterial microbes. The results showed that employing INH magnetic nano particles and INH magnetic nano particles respectively reduced the minimum inhibitory concentration of INH in conjugation with MNPs to 44.8% and 16.7%. Additionally, antimicrobial analysis of the samples demonstrated that pure INH had no inhibitory effects against non-mycobacterial strains up to 500μg/ml additionally combining isoniazid with magnetic nano particles may result in a notable antibacterial action against non mycobacterial strains in addition to enhancing the anti mycobacterial activity [22].

3. Drug Profile [23]

3.1 Isoniazid

Background: Isoniazid is one of the most potent anti-tuberculosis drugs. Isoniazid is used in first line treatment and to prevent latent TB from progressing.

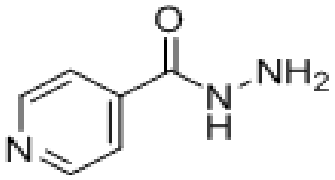
IUPAC name: pyridine-4-carboxylic acid hydrazide

Synonym: Isonicotinic acid hydrazide.

Molecular weight: 137.14g/mol

Molecular formula: $C_6H_7N_3O$

Structural formula:



Solubility: Very soluble in water, practically insoluble in ether and benzene.

Melting point: 171°-173°C

Dissociation constant: pka = 1.8

Partition coefficient: 0.64

Mechanism of action of Isoniazid: Since 1952, isoniazid has been a key component of TB treatment plans. The catalase-peroxidase KatG activates the pro drug INH forming a range of radicals and adducts that prevent them Mycobacterium from producing them mycolic acids that comprise its cell wall. INH has the capacity to be a strong bactericidal agent because of its activity. Additionally the medicine seems to work in concert with other TB-treating drugs and other species that KatG produces.

Side effects: More common: Clumsiness or unsteadiness, dark urine, loss of appetite, nausea or vomiting, numbness, tingling, burning, or pain in hands and feet, unusual tiredness or weakness, yellow eyes or skin

Rare: Blurred vision or loss of vision with or without eye pain. Convulsions (seizures) fever and sore throat joint pain mental expression mood or other mental changes.

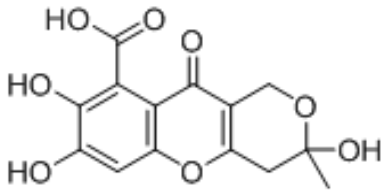
3.2 Fulvic Acid (24)

Source: Naturally occurring organic acid derived from humic substances.

Chemical Name: 3,7,8-trihydroxy-3-methyl-10-oxo-1,4-dihydropyrano[4,3-b] chromene-9-carboxylic acid

Molecular Formula: $C_{14}H_{12}O_8$

Molecular Structure



Melting point: 246-247℃

Solubility: Highly soluble

Pharmacological Properties:

- Bio enhancer: Increases permeability and absorption of co-administered drugs
- Immunomodulator**:** Enhances local immune response
- Antioxidant &anti-inflammatory effects

Advantages in Formulation: Natural compound with low toxicity Promotes localized effect can contribute to prolonged action in mucoadhesive systems.

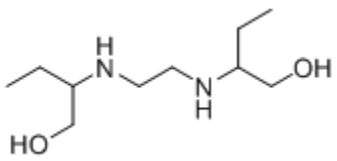
3.3 Ethambutol

Source: Synthetic antitubercular drug (first-line agent for TB)

Chemical Name: ***(2R,2'R)-2,2'-(ethane-1,2-diyldiimino)di-1-butanol***

Molecular Formula: $C_{10}H_{24}N_2O_2$ (base)

Molecular Structure



Melting Point: 198–200°C

Solubility: Highly soluble in water**, f**reely soluble in alcohol and insoluble in non-polar solvents

Mechanism of Action in Ethambutol

Ethambutol exerts its antimycobacterial action by inhibiting the arabinosyl transferase enzymes EmbA and EmbB which are essential for the synthesis of arabinan a key structural component of the mycobacterial cell wall. Inhibition of arabinan formation disrupts the integrity of the cell wall leading to increased permeability impaired cell wall assembly and subsequent inhibition of mycobacterial replication. Owing to this mechanism ethambutol plays an important role in preventing the emergence of drug resistance and enhances the overall bactericidal activity of first-line anti-tubercular regimens. It is particularly effective when used in combination with isoniazid, rifampicin and pyrazinamide forming a synergistic therapeutic regimen that improves treatment outcomes in tuberculosis including extra-pulmonary forms such as gastrointestinal TB [25].

Pharmacokinetics

Parameters	**Details**
• Absorption	Rapid and well absorbed orally
• Bioavailability	High not significantly affected by food
• Peak Plasma Time	Reaches maximum plasma concentration in 2-4 hours after oral intake.
• Distribution	Widely distributed in body tissues including lungs crosses the blood brain barrier if meninges are inflamed
• Protein binding	Low~20-30%
• Metabolism	Minimal hepatic metabolism
• Excretion	Primarily via kidney (Renal route)
• Elimination	50-80% excreted unchanged in urine minorfecal excretion
• Half life	3-4 hours (prolong renal impairment)
• Volume of Distribution	1.6l/kg

4. Background & Rationale

Gastric TB is a rare but clinically important manifestation of extra pulmonary TB. Standard oral therapy suffers from poor gastric retention, systemic side effects, hepatotoxicity and limited local action. Mucoadhesive tablets provide prolonged gastric residence and controlled release, increasing local concentration of drugs and reducing systemic toxicity. Isoniazid is first line anti TB drug but rapid systemic clearance and hepatotoxicity limit effectiveness at the gastric site.

Fulvic Acid is a natural organic acid with bio enhancing properties (increases solubility, permeability and absorption). Also reported to have immune modulatory and anti microbial effects.

Ethambutol is a first-line antitubercular medication introduced in the early 1960s to improve the efficacy and safety of tuberculosis treatment. it is valued for its low toxicity compared with alternative agents its oral availability and its synergistic activity with isoniazid, rifampicin, and pyrazinamide.

Therefore from literature review it was observed that Co-loading of isoniazid with fulvic acid and ethambutol with fulvic acid in a mucoadhesive system may improve site specific action, lower systemic dose and enhance anti-TB efficacy.

5. Aim and Objective

To formulate and evaluate a combinational drug therapy based mucoadhesive tablet for targeted, sustained and enhanced therapeutic management of gastric tuberculosis.

Objectives

- To develop mucoadhesive tablet formulations in corporating isoniazid and fulvic acid, ethambutol and fulvic acid using suitable polymers and excipients.
- To optimize the drug polymer ratio for achieving desired mucoadhesive strength and sustained release properties.
- To assess the potential synergistic effects of combining isoniazid with fulvic acid and isoniazid and ethambutol in enhancing the anti-tubercular activity and mucosal healing.
- To evaluate the physiochemical properties of the formulated tablets including hardness, thickness, weight variation, friability and swelling index.
- To determine the mucoadhesive strength and residence time of tablets using appropriate *in-vitro* mucoadhesive models.
- To study the *in-vitro* drug release profile and release kinetics of isoniazid, fulvic acid and ethambutol from mucoadhesive tablets.
- To evaluate the stability of the optimized formulation as per ICH guidelines.

6. Plan of Work

The study shall be carried out on the following lines.

6.1. Extensive Literature review

6.2 Procurement of the drugs and chemicals

6.3 Pre-formulation profiling

- Identification APIs by UV, FT-IR
- Solubility analysis
- Melting point
- Partition coefficient
- Drug-Excipients Compatibility Study

6.4 Evaluation of synergistic combination of Isoniazid and Fulvic Acid, Ethamutol and Fulvic Acid by using Alamar Blue Assay against GI Tuberculosis.

6.5 Calculation of combinational dose index by Chou Talalay Method

6.6 Formulation of mucoadhesive tablet by direct compression method

6.7 Optimization of mucoadhesive tablet by response surface methodology

6.8 Evaluation of Mucoadhesive Tablets

- Pre-compression parameters
- Flow property of powder blend
- Post-compression parameters
    - ✓ Tablet thickness and hardness
    - ✓ Weight variation test
    - ✓ Percentage friability
    - ✓ Wetting time
    - ✓ Water absorption ratio
    - ✓ Swelling index
    - ✓ In-vitro Muco-adhesion Strength
    - ✓ In-vitro Muco-adhesion Time

- ✓ *In Vitro* drug release study

- *In-vitro* drug release kinetics
- Stability Studies as per ICH guideline

6.9 Compilation of Results

6.10 Paper Publications

6.11 Submission of the thesis

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